Prediction of small for gestational age neonates at 35-37 weeks' gestation: Contribution of maternal factors and growth velocity between 32 and 36 weeks

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ABSTRACT

Objective: To assess the additive value of fetal growth velocity between 32 and 36 weeks' gestation on the performance of ultrasonographic estimated fetal weight (EFW) at 35^{+0} - 36^{+6} weeks' gestation for prediction of small for gestational age (SGA) neonates and adverse perinatal outcome.

Methods: This was a prospective study of 14,497 singleton pregnancies that had undergone routine ultrasound examination at 28^{+0} - 34^{+6} and at 35^{+0} - 36^{+6} weeks' gestation. Multivariable logistic regression analysis was used to determine whether addition of growth velocity, defined by a difference in EFW and abdominal circumference (AC) Z-scores between the early and late third trimester scans divided by the time interval between them, improved the performance of EFW at 35^{+0} - 36^{+6} weeks in the prediction of first, delivery of SGA neonates with birthweight <10th and <3rd percentiles within two weeks and at any stage after assessment and second, composite of adverse perinatal outcome defined as stillbirth, neonatal death or admission to the neonatal unit for ≥48 hours.

Results Multivariable logistic regression analysis demonstrated that significant contributors to prediction of SGA neonates were EFW Z-score at 35^{+0} - 36^{+6} weeks' gestation, fetal growth velocity by either AC or EFW Z-scores and maternal risk factors. The area under the receiver operating characteristic curves (AUROC) and detection rate (DR) with 95% confidence interval, at 10% screen positive rate, for prediction of SGA neonates <10th percentile born within two weeks of assessment achieved by EFW Z-score at 35^{+0} - 36^{+6} weeks (AUROC 0.938, 0.928 - 0.947; DR 80.7, 77.6 - 83.9) were not significantly improved by addition of EFW growth velocity and maternal risk factors (AUROC 0.941, 0.932 - 0.950; p=0.061; DR 82.5, 79.4 - 85.3). Similar results were obtained when growth velocity was defined by AC rather than EFW growth velocity. Similarly, there was no significant improvement in AUROC and DR, at 10% screen positive rate, for prediction of SGA neonates <10th percentile born at any stage after assessment or SGA neonates <3rd percentile born within two weeks or at any stage after assessment achieved by EFW Z-score at 35^{+0} - 36^{+6} weeks by addition of maternal factors and either EFW growth velocity of AC growth velocity. Multivariable logistic regression analysis demonstrated that the only significant contributor to adverse perinatal outcome was maternal risk factors. Multivariable logistic regression analysis in the group with EFW <10th percentile demonstrated that significant contribution to prediction of birth of neonates with birthweight <10th and <3rd percentiles and adverse perinatal outcome was provided by EFW Z-score at 35^{+0} - 36^{+6} weeks, but not by AC growth velocity <1st decile.

Conclusion: The predictive performance of EFW at 35^{+0} - 36^{+6} weeks' gestation for birth of SGA neonates and adverse perinatal outcome is not improved by addition of estimated growth velocity between 32 and 36 weeks' gestation.

INTRODUCTION

Several studies have reported on prenatal diagnosis and management of small for gestational age (SGA) fetuses.[1-13] These studies have established that: first, the predictive performance of the traditional method of identifying pregnancies with SGA fetuses, maternal abdominal palpation and serial measurements of symphysial-fundal height, is poor;[1,3] second, substantially improved prediction of SGA is achieved by universal sonographic fetal biometry during the third trimester;[8-12] and third, about 85% of SGA neonates are born at $\geq$37 weeks' gestation,[14] and the predictive performance of routine ultrasonography at 36 weeks' gestation is superior to that at 32 weeks.[8,9,11]

Although the performance of routine ultrasonographic estimated fetal weight (EFW) at 36 weeks' gestation is superior to that of other methods this requires further improvement. One approach aiming for such improvement in predictive performance of the 36 week's scan is to combine EFW with maternal demographic characteristics and medical history; two studies reported that with the addition of maternal risk factors prediction of SGA neonates born at any stage after assessment was improved from 63% to about 67%, at screen positive rate of 10%.[9,15] Further improvement in prediction to about 70% can be achieved with the addition of serum placental growth factor and uterine artery and middle cerebral artery pulsatility index.[14] Another approach for improvement in the prediction of SGA neonates and adverse perinatal outcome provided by fetal biometry is fetal growth velocity; however, previous studies investigating the potential value of fetal growth velocity reported contradictory results.[15-21] In a study of 44,043 singleton pregnancies that had undergone routine ultrasound examination at $19^{+0} - 23^{+6}$ and at $35^{+0} - 36^{+6}$ weeks' gestation, we found that the predictive performance of EFW at $35^{+0} - 36^{+6}$ was not improved by addition of estimated growth velocity between the second and third trimesters of pregnancy.[15] A possible explanation for such failure is the long interval between the two ultrasound examinations that defined growth velocity and the proximity of the second scan to delivery which would inevitably minimize the contribution of growth velocity to that of EFW at $35^{+0} - 36^{+6}$ weeks.

The objective of this study is to assess the additive value of fetal growth velocity between 32 and 36 weeks' gestation on the performance of ultrasonographic EFW at $35^{+0} - 36^{+6}$ weeks' gestation for prediction of SGA neonates and adverse perinatal outcome.

METHODS

The inclusion criteria for this study were singleton pregnancies that had undergone routine ultrasound examination at $35^{+0} - 36^{+6}$ weeks' gestation, had a previous scan at least two weeks earlier at $30^{+0} - 34^{+6}$ weeks and delivered a non-malformed live birth or stillbirth. We excluded pregnancies with aneuploidies and major fetal abnormalities. The women were examined at King's College Hospital, London or Medway Maritime Hospital, Gillingham, UK between October 2013 and September 2018. We recorded maternal demographic characteristics and medical history and carried out the two ultrasound examinations for fetal anatomy and measurement of fetal head circumference (HC), AC and femur length (FL) for calculation of EFW by the Hadlock formula, which has been shown to be the most accurate one among 70 previously reported models.[22,23] Gestational age was determined by the measurement of fetal crown-rump length at 11-13 weeks or the fetal head circumference at 19-24 weeks.[24,25] The ultrasound examinations were carried out by examiners who had obtained the Fetal Medicine Foundation certificate of competence in ultrasound examination for fetal abnormalities. The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

Patient characteristics

Patient characteristics recorded included maternal age, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (natural, *in vitro* fertilization or use of ovulation induction drugs), cigarette smoking during pregnancy, medical history of chronic hypertension and diabetes mellitus, obstetric history including parity (parous or nulliparous if no previous pregnancies at $\geq$ 24 weeks' gestation), and previous pregnancy with SGA. The maternal weight and height were measured.

Outcome measures

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The outcome measures of the study were first, delivery of SGA neonates with birthweight <10th and <3rd percentiles for gestational age at delivery,[26] within two weeks and at any stage after assessment, and second, composite of adverse perinatal outcome defined as stillbirth, neonatal death and admission to the neonatal unit for ≥48 hours.

Statistical analysis

Data were expressed as median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Mann-Whitney U-test and χ^2-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively. Significance was assumed at 5%.

In the dataset of 14,497 singleton pregnancies with paired measurements of fetal biometry at 30^{+0} - 34^{+6} and 35^{+0} - 36^{+6} weeks' gestation, the observed measurements of AC and EFW were expressed as Z-scores for gestational age.[25,26] Fetal growth velocity was defined as the difference in AC Z-scores and EFW Z-scores between the two ultrasound scans divided by the time interval in days between them. Univariable and multivariable regression analysis was carried out to determine whether the addition of AC and EFW growth velocity and maternal factors to the EFW Z-score at 35^{+0} - 36^{+6} weeks' gestation improved the performance of screening for first, SGA neonates <10th and <3rd percentile delivering within two weeks and at any stage after assessment, and second, adverse perinatal outcome. In prediction of the adverse outcomes, we assumed the relationship between the dependent and independent variables to be linear as the evaluation of growth velocity was only between gestational window of 32 and 36 weeks' gestation. The *a priori* risk for SGA based on maternal factors was derived from a dataset of 124,443 singleton pregnancies at 11^{+0} - 13^{+6} weeks' gestation using multivariable logistic regression analysis with backward stepwise elimination to determine which of the factors among maternal characteristics and medical and obstetric history had a significant contribution in predicting SGA <10th.[14] Regression analysis was also carried out in the group with EFW <10th percentile to determine whether EFW Z-score at 35^{+0} - 36^{+6} weeks' gestation and AC growth velocity <1st decile had a significant contribution in the prediction of first, SGA neonates <10th and <3rd percentile delivering at any stage after assessment, and second, adverse perinatal outcome. The performance of screening was determined by receiver operating characteristic (ROC) curves. We estimated detection rates (DR) with 95% confidence intervals (CI) for fixed screen positive rate of 10% and screen positive rates (95% CI) for fixed DRs of 85%, 90% and 95%.

The statistical software package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for data analyses.

RESULTS

Patient characteristics

During the study period 44,043 singleton pregnancies had undergone routine ultrasound examination at 35^{+0} - 36^{+6} weeks' gestation. Search of our fetal database identified 14,497 of these 44,043 pregnancies that had undergone an additional ultrasound examination at least two weeks earlier at 30^{+0} - 34^{+6} weeks. The indications for the ultrasound scan at 30^{+0} - 34^{+6} weeks included: (a) high risk of preeclampsia (PE) and / or SGA because of abnormal screening results in the first or second trimester of pregnancy, such as low serum PAPP-A, high uterine artery PI or single umbilical artery (27.8%); (b) previous pregnancy complications, such as perinatal death, abruption, PE and / or SGA (11.4%); (c) maternal medical disorders, such as chronic hypertension, antiphospholipid syndrome, diabetes mellitus or hypothyroidism (11.7%); (d) pregnancy complications, such as PE, gestational diabetes mellitus, or cholestasis (9.1%); (e) small or big symphysial-fundal height (11.9%), increased maternal age or weight (9.0%); reduced fetal movements (7.0%); (f) minor fetal defects, such as mild ventriculomegaly, or mild hydronephrosis (5.0%); (g) low lying placenta and / or antepartum hemorrhage (6.2%); and (h) increased risk of preterm birth due to abdominal pain, reduced cervical length or history of previous preterm birth (0.9%).

The characteristics of the study population of 14,497 pregnancies are shown in Table 1. In the group with SGA neonates, compared to those with birthweight ≥10th percentile, the median maternal age, weight and height, EFW Z-score at both visits and birthweight z-score were lower, more women were of non-White racial origin, were smokers, were nulliparous or parous with previous affected pregnancy by SGA, and less women had diabetes mellitus type 1 or type 2. The incidence of adverse perinatal outcome was significantly higher in the SGA than in the non-SGA group (12.8% vs. 8.6%; p<0.001).

Prediction of SGA neonates

Multivariable logistic regression analysis demonstrated that significant contributors to prediction of SGA neonates were EFW Z-score at 35^{+0} - 36^{+6} weeks' gestation, fetal growth velocity by either AC or EFW Z-scores and maternal risk factors (Table 2). The area under the receiver operating characteristic curves (AUROC) for prediction of SGA neonates <10th percentile born within two weeks of assessment achieved by EFW Z-score at 35^{+0} - 36^{+6} weeks were not significantly improved by addition of EFW growth velocity and maternal risk factors (0.938, 0.928 - 0.947 vs. 0.941, 0.932 - 0.950; p=0.061) (Table 3, Figure 1). Similarly, there were no statistically significant differences in DR, at 10% screen positive rate, in screening with and without the addition of EFW growth velocity and maternal risk factors (Table 3); similar results were obtained when growth velocity was defined by AC Z-score. There was no significant improvement in AUROC and DR, at 10% screen positive rate, for prediction of SGA neonates <10th percentile born at any stage after assessment or SGA neonates <3rd percentile born within two weeks or at any stage after assessment achieved by EFW Z-score at 35^{+0} - 36^{+6} weeks by addition of maternal risk factors and either EFW growth velocity of AC growth velocity.

The screen positive rates necessary to achieve prediction of 85%, 90% and 95% of SGA neonates born within two weeks and at any stage after assessment at 35^{+0} – 36^{+6} weeks' gestation are shown in Table 4. For a desired 90% prediction of SGA neonates <10th percentile born at any stage after assessment the necessary screen positive rate would be 30.7% (95% CI 29.9 - 31.5%) in screening by EFW Z-score at 35^{+0} - 36^{+6} weeks and 29.8% (95% CI 29.0 - 30.6%) in screening by EFW Z-score, AC growth velocity and maternal risk factors.

Prediction of adverse perinatal outcome

The incidence of adverse perinatal outcome in the study population was 9.2% (1,336/14,497). The contribution of SGA neonates with birthweight <10th percentile to adverse perinatal outcome was 21.7% (290/1,336). Multivariable logistic regression analysis in the whole population demonstrated that the only significant contributor to adverse perinatal outcome was maternal risk factors (Table 2).

Prediction in the group with EFW <10th percentile

Multivariable logistic regression analysis in the group with EFW <10th percentile demonstrated that significant contribution to prediction of birth of neonates with birthweight <10th and <3rd percentiles and adverse perinatal outcome was provided by EFW Z-score at 35^{+0} - 36^{+6} weeks, but not by AC growth velocity <1st decile (Table 5).

DISCUSSION

Main findings of the study

The findings of this study demonstrate that although significant contributors to prediction of SGA neonates were EFW Z-score at 35^{+0} - 36^{+6} weeks' gestation, fetal growth velocity between 32 and 36 weeks by either AC or EFW Z-scores and maternal risk factors, the predictive performance of EFW was not improved by the addition of growth velocity and maternal risk factors. The incidence of adverse perinatal outcome was higher in SGA than in non-SGA neonates (12.8% vs. 8.6%), but about 80% of adverse perinatal events occurred in non-SGA neonates. The only significant contributor to adverse perinatal outcome was maternal risk factors. Multivariable logistic regression analysis in the group with EFW <10th percentile demonstrated that significant contribution to prediction of birth of SGA neonates and adverse perinatal outcome was provided by EFW Z-score at 35^{+0} - 36^{+6} weeks, but not by AC growth velocity <1st decile.

Comparison with findings from previous studies

Previous studies have investigated the effect of fetal growth velocity on prediction of first, birth of SGA neonates and second, adverse perinatal outcome. In relation to prediction of birth of SGA neonates, our finding that the performance of EFW is not improved by the addition of growth velocity is consistent with the results of previous studies. Tarca *et al.,* examined 3,440 pregnancies and reported that serial fetal biometry did not improve the prediction of SGA neonates provided by the last EFW before delivery alone.[16] Caradeux *et al.,* examined 2,696 pregnancies at 22 and 32 weeks' gestation and reported that the growth velocity in AC between 22 and 32 weeks did not improve the prediction of SGA neonates provided by AC at 32 weeks.[17] Ciobanu *et al.,* examined 44,043 singleton pregnancies that had undergone routine ultrasound examination at 19^{+0} - 23^{+6} and at 35^{+0} - 36^{+6} weeks' gestation and reported that the predictive performance for SGA neonates provided by EFW in the third trimester is not improved by addition of estimated growth velocity between the second and third trimesters of pregnancy.[15]

In relation to prediction of adverse perinatal outcome, previous studies examined the effect of growth velocity or conditional growth in SGA fetuses rather than in the total population. Sovio *et al.,* reported that in 562 SGA fetuses with EFW <10th percentile during a third trimester scan, low growth velocity below the 1st decile in fetal AC between 20 weeks' gestation and the last scan before delivery had a higher prevalence of adverse perinatal outcome, compared to those without such a degree of decrease in growth velocity (15.7% vs. 10.3%; p=0.01); however, the authors did not present evidence that growth velocity improved the performance of screening for adverse

perinatal outcome achieved by EFW percentile alone.[12] Karlsen *et al.,* performed serial ultrasound scans in 211 pregnancies with suspected SGA fetuses and reported that growth velocity improved the prediction of adverse perinatal outcome provided by cross sectional measurements of fetal biometry.[18] In contrast, Cavallaro *et al.,* reported that in 235 SGA fetuses diagnosed at 36-38 weeks' gestation low growth velocity in fetal AC between 19-21 and 36-38 weeks did not improve the prediction of adverse perinatal outcome provided by EFW and cerebroplacental ratio at 36-38 weeks (AUROC 0.741 vs 0.669; p=0.110).[19] Similarly, Hutcheon *et al.,* used the EFW in 9,239 singleton pregnancies undergoing routine ultrasound examination at 32-33 weeks' gestation to predict birthweight and reported that deviations between expected and observed birthweights, attributed to varying growth velocities between the scan and delivery, did not improve the prediction of adverse outcome of SGA neonates provided by their birthweight percentile alone.[20] Caradeux *et al.,* examined longitudinally 472 SGA fetuses diagnosed >32 weeks' gestation and reported that in subsequent scans growth velocity in EFW did not improve the prediction of adverse perinatal outcome provided by EFW, uterine artery pulsatility index and cerebroplacental ratio recorded in the last scan before delivery.[21]

Implications for clinical practice

Several studies have reported first, how best to monitor and deliver SGA neonates,[2,5-7] second, that about 85% of SGA neonates are born at ≥37 weeks' gestation and third, the best prediction of SGA neonate is achieved by routine ultrasound examination at 36 week's gestation.[8,9,11,12,14] This findings of this study have highlighted the necessity to improve the performance of the 36 weeks' assessment in the prediction of both birth of SGA neonates and adverse perinatal outcome and have demonstrated that these goals cannot be achieved by addition of fetal growth velocity between 32 and 36 weeks' gestation to EFW at 36 weeks.

Strengths and limitations of the study

The strengths of this screening study for SGA neonates are first, examination of a large population of pregnant women attending for assessment of fetal growth and wellbeing at both 30^{+0} - 34^{+6} and 35^{+0} - 36^{+6} weeks' gestation, second, trained sonographers that carried out fetal biometry according to a standardized protocol and use of a widely used model for calculation of EFW[22] which has been shown to be the most accurate one among 70 previously reported models,[23] third, use of the Fetal Medicine Foundation fetal and neonatal references ranges which have a common median,[26] and fourth, use of well accepted indicators for adverse perinatal outcome.

A potential limitation of the study is the selection of patients undergoing the two ultrasound examinations. During the study period we offered routine ultrasound examinations at 11^{+0} - 13^{+6}, 19^{+0} - 23^{+6} and at 35^{+0} - 36^{+6} weeks' gestation, whereas a scan at 30^{+0} - 34^{+6} weeks was offered only to women considered to be at increased risk of fetal growth disturbances or adverse outcome based on their demographic characteristics, medical history, results of first or second trimester screening for preeclampsia, small or large symphysial-fundal height and pregnancy complications. As a consequence of such preselection the predictive performance of EFW at 35^{+0} - 36^{+6} weeks' gestation for SGA neonates and adverse perinatal outcome may not be the same as in an unselected population. However, the objective of the study was to examine the effect of growth velocity on the performance of the EFW at 35^{+0} - 36^{+6} and in this respect the results are valid. A limitation of the study is the assumption of the linear relationship between dependent and independent variables in regression analysis. Linear relationship was assumed as we examined the growth velocity in the narrow gestational window between 32 and 36 weeks' gestation.

Conclusions

The predictive performance of EFW at 35^{+0} - 36^{+6} weeks' gestation for birth of SGA neonates and adverse perinatal outcome is not improved by addition of estimated growth velocity between 32 and 36 weeks' gestation. The incidence of adverse perinatal outcome is higher in SGA than in non-SGA neonates, but only about one-fifth of adverse perinatal events are found in association with SGA neonates. Future studies will investigate the potential improvement in prediction of adverse perinatal outcome by biomarkers of impaired placentation at the time of the 36 weeks' assessment.

REFERENCES

1. Lindhard A, Nielsen PV, Mouritsen LA, Zachariassen A, Sørensen HU, Rosenø H. The implications of introducing the symphyseal-fundal height-measurement. A prospective randomized controlled trial. Br J Obstet Gynaecol 1990;97:675-80.

2. Baschat AA, Gembruch U, Harman CR. The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 2001;18:571-7.

3. Bais JMJ, Eskes M, Pel M, Bonsel GJ, Bleker OP. Effectiveness of detection of intrauterine retardation by abdominal palpation as screening test in a low-risk population: an observational study. Eur J Obstet Gynecol Reprod Biol 2004;116:164-9.

4. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol 2005;25:258-64.

5. Baschat AA, Galan HL, Bhide A, Berg C, Kush ML, et al. Doppler and biophysical assessment in growth restricted fetuses: distribution of test results. Ultrasound Obstet Gynecol 2006;27:41-7.

6. Figueras F, Caradeux J, Crispi F, Eixarch E, Peguero A, Gratacos E. Diagnosis and surveillance of late-onset fetal growth restriction. Am J Obstet Gynecol 2018;218:S790-S802.e1

7. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 2018;218:S855-S868.

8. Bakalis S, Silva M, Akolekar R, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: screening by fetal biometry at 30–34 weeks. Ultrasound Obstet Gynecol 2015;45:551-8.

9. Fadigas C, Saiid Y, Gonzalez R, Poon LC, Nicolaides KH. Prediction of small for gestational age neonates: screening by fetal biometry at 35-37 weeks. Ultrasound Obstet Gynecol 2015;45:559-65.

10. Poon LC, Lesmes C, Gallo DM, Akolekar R, Nicolaides KH. Prediction of small-for-gestational-age neonates: screening by biophysical and biochemical markers at 19-24 weeks. Ultrasound Obstet Gynecol 2015;46:437-45.

11. Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F. Ultrasound screening for fetal growth restriction at 36 vs 32 weeks' gestation: a randomized trial (ROUTE). Ultrasound Obstet Gynecol 2015;46:391-7.

12. Sovio U, White IR, Dacey A, Pasupathy D, Smith GCS. Screening for fetal growth restriction with universal third trimester ultrasonography in nulliparous women in the Pregnancy Outcome Prediction (POP) study: a prospective cohort study. Lancet 2015;386:2089-2097.

13. Triunfo S, Crispi F, Gratacos E, Figueras F. Prediction of delivery of small-for-gestational-age neonates and adverse perinatal outcome by fetoplacental Doppler at 37 weeks' gestation. Ultrasound Obstet Gynecol 2017;49:364-71.

14. Ciobanu A, Rouvali, A, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates: Screening by maternal factors, fetal biometry and biomarkers at 35-37 weeks' gestation. Am J Obstet Gynecol (in press).

15. Ciobanu A, Formuso C, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of small for gestational age neonates at 35-37 weeks' gestation: Contribution of maternal factors and growth velocity between 20 and 36 weeks. Ultrasound Obstet Gynecol 2019; in press

16. Tarca AL, Hernandez-Andrade E, Ahn H, Garcia M, Xu Z, Korzeniewski SJ, Saker H, Chaiworapongsa T, Hassan SS, Yeo L, Romero R. Single and serial fetal biometry to detect preterm and term small- and large-for-gestational-age neonates: a longitudinal cohort study. PLoS One 2016;11:e0164161.

17. Caradeux J, Eixarch E, Mazarico E, Basuki TR, Gratacós E, Figueras F. Second- to third-trimester longitudinal growth assessment for prediction of small-for-gestational age and late fetal growth restriction. Ultrasound Obstet Gynecol 2018;51:219-224.

18. Karlsen HO, Johnsen SL, Rasmussen S, Kiserud T. Prediction of adverse perinatal outcome of small-for-gestational-age pregnancy using size centiles and conditional growth centiles. Ultrasound Obstet Gynecol 2016;48:217-23.

19. Cavallaro A, Veglia M, Svirko E, Vannuccini S, Volpe G, Impey L. Using fetal abdominal circumference growth velocity in the prediction of adverse outcome in near-term small-for-gestational-age fetuses. Ultrasound Obstet Gynecol 2018;52:494-500.

20. Hutcheon JA, Egeland GM, Morin L, Meltzer SJ, Jacobsen G, Platt RW. The predictive ability of conditional fetal growth percentiles. Paediatr Perinat Epidemiol 2010;24:131-9.

21. Caradeux J, Eixarch E, Mazarico E, Basuki TR, Gratacos E, Figueras F. Longitudinal growth assessment for prediction of adverse perinatal outcome in fetuses suspected to be small-for-gestational age. Ultrasound Obstet Gynecol 2018;52:325-331.

22. Hadlock FP. Harrist RB. Sharman RS. Deter RL. Park SK. Estimation of fetal weight with the use of head, body, and femur measurements–a prospective study. *Am J Obstet Gynecol* 1985; **151:** 333-337.

23. Hammami A, Mazer Zumaeta A, Syngelaki A, Akolekar R, Nicolaides KH. Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models. Ultrasound Obstet Gynecol 2018;52:35-43.

24. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. Br J Obstet Gynaecol 1975;82:702-10.

25. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol 1994;4:34-48.

26. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. Ultrasound Obstet Gynecol 2018;52:44-51.

FIGURE LEGENDS

Figure 1. Receiver operating characteristics curves of maternal risk factors (black curve), estimated fetal weight at 35^{+0} - 36^{+6} weeks' gestation (blue curve), estimated fetal weight growth velocity (green curve), and the combination of the three (red curve) in the prediction of small for gestational age neonates with birth weight below the 10th percentile delivering within two weeks (left) and at any time (right) from assessment.

Table 1- Maternal and pregnancy characteristics in pregnancies delivering small for gestational age neonates <10th percentile and those without.

Characteristic	BW ≥10th percentile (n=12,216)	BW <10th percentile (n=2,281)	P-value
Maternal age in years, median (IQR)	32.2 (27.8-36.1)	31.2 (26.5-35.3)	<0.001
Maternal weight in Kg, median (IQR)	81.6 (72.0-94.3)	74.0 (65.6-85.0)	<0.001
Maternal height in cm, median (IQR)	165 (160-169)	163 (158-167)	<0.001
Racial origin			
White, n (%)	8,917 (73.0)	1,428 (62.6)	<0.001
Black, n (%)	2,142 (17.5)	515 (22.6)	<0.001
South Asian, n (%)	573 (4.7)	214 (9.4)	<0.001
East Asian, n (%)	228 (1.9)	51 (2.2)	0.238
Mixed, n (%)	356 (2.9)	73 (3.2)	0.459
Cigarette smoker, n (%)	942 (7.7)	337 (14.8)	<0.001
Conception			
Natural, n (%)	11,693 (95.7)	2,190 (96.0)	
Ovulation drugs, n (%)	71 (0.6)	14 (0.6)	0.852
In vitro fertilization, n (%)	452 (3.7)	77 (3.4)	0.448
Medical conditions			
Chronic hypertension, n (%)	383 (3.1)	71 (3.1)	0.955
Diabetes mellitus type 1, n (%)	161 (1.3)	1 (0.04)	<0.001
Diabetes mellitus type 2, n (%)	215 (1.8)	22 (1.0)	0.006
Past obstetric history			
Nulliparous, n (%)	4,848 (39.7)	1,154 (50.6)	<0.001
Parous with prior SGA, n (%)	1,218 (10.0)	529 (23.2)	<0.001
Parous without prior SGA, n (%)	6,150 (50.3)	598 (26.2)	<0.001
GA at screening at $30^{+0} - 34^{+6}$ weeks, median (IQR)	32.3 (31.9-32.6)	32.3 (31.9-32.7)	<0.001
EFW Z-score at $30^{+0} - 34^{+6}$ weeks, median (IQR)	0.21 (-0.43-0.89)	-1.11 (-1.79- -0.51)	<0.001
AC Z-score at $30^{+0} - 34^{+6}$ weeks, median (IQR)	0.04 (-0.40-0.50)	-0.76 (-1.19- -0.37)	<0.001
GA at screening at $35^{+0}-36^{+6}$ weeks, median (IQR)	36.1 (35.9-36.4)	36.1 (35.9-36.4)	0.020
EFW Z-score at $35^{+0}-36^{+6}$ weeks, median (IQR)	0.17 (-0.47-0.82)	-1.44 (-2.14- -0.78)	<0.001
AC Z-score at $35^{+0} - 36^{+6}$ weeks, median (IQR)	-0.06 (-0.56-0.47)	-1.18 (-1.17- -0.70)	0.001
GA at delivery in weeks, median (IQR)	39.6 (38.9-40.6)	39.1 (38.0-40.1)	<0.001
Birthweight Z-score, median (IQR)	0.07 (-0.53-0.71)	-1.79 (-2.25- -1.51)	<0.001
Birthweight in grams, median (IQR)	3422 (3155-3725)	2655 (2440-2820)	<0.001
Adverse perinatal outcome, n (%)	1,046 (8.6)	290 (12.8)	<0.001

BW = birth weight; GA = gestational age; EFW = estimated fetal weight; IQR = interquartile range; SGA = small for gestational age

Table 2. Multivariable logistic regression analysis in prediction of small for gestational age neonates <10th and <3rd percentiles and adverse perinatal outcome from maternal risk factors, estimated fetal weight Z-score at 35^{+0} – 36^{+6} weeks' gestation and estimated fetal weight growth velocity (top table) or abdominal circumference growth velocity (bottom table).

Characteristic	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Birthweight <10th percentile				
Maternal risk factors	13.55 (11.49-15.99)	<0.001	5.77 (4.71-7.07)	<0.001
EFW z-score	0.17 (0.16-0.18)	<0.001	0.17 (0.16-0.18)	<0.001
EFW growth velocity	$3.01e^{-7}$ ($5.44e^{-8}$-$2.01e^{-6}$)	<0.001	$1.25e^{3}$ ($1.19e^{2}$-$1.32e^{4}$)	<0.001
Birthweight <3rd percentile				
Maternal risk factors	13.80 (10.94-17.40)	<0.001	4.46 (3.37-5.92)	<0.001
EFW z-score	0.17 (0.15-0.18)	<0.001	0.16 (0.15-0.18)	<0.001
EFW growth velocity	$3.43e^{-8}$ ($3.28e^{-9}$-$3.60e^{-7}$)	<0.001	$7.09e^{3}$ ($3.16e^{2}$-$1.59e^{5}$)	<0.001
Adverse perinatal outcome				
Maternal risk factors	0.66 (0.50-0.87)	0.004	0.66 (0.50-0.87)	0.004
EFW z-score	0.97 (0.91-1.03)	0.282		
EFW growth velocity	0.48 (0.02-11.09)	0.645		

Characteristic	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Birthweight <10th percentile				
Maternal risk factors	13.55 (11.49-15.99)	<0.001	5.74 (4.69-7.03)	<0.001
EFW z-score	0.17 (0.16-0.18)	<0.001	0.17 (0.15-0.18)	<0.001
AC growth velocity	$8.04e^{-12}$ ($9.33e^{-13}$-$6.92e^{-11}$)	<0.001	$5.80e^{3}$ ($2.85e^{2}$-$1.18e^{5}$)	<0.001
Birthweight <3rd percentile				
Maternal risk factors	13.80 (10.94-17.40)	<0.001	4.46 (3.37-5.92)	<0.001
EFW z-score	0.17 (0.15-0.18)	<0.001	0.16 (0.15-0.18)	<0.001
AC growth velocity	$1.76e^{-13}$ ($9.09e^{-15}$-$3.40e^{-12}$)	<0.001	$3.10e^{3}$ ($0.58e^{2}$-$1.64e^{5}$)	<0.001
Adverse perinatal outcome				
Maternal risk factors	0.66 (0.50-0.87)	0.004	0.66 (0.50-0.87)	0.004
EFW z-score	0.97 (0.91-1.03)	0.282	-	-
AC growth velocity	15.18 (0.37-626.41)	0.152	-	-

EFW = estimated fetal weight; AC = Abdominal circumference; OR = odds ratio; CI = confidence interval; SGA = small for gestational age

Table 3. Performance of prediction of small for gestational age neonates with birth weight <10th, and <3rd percentile delivering within two weeks and at any stage after screening at $35^{+0} – 36^{+6}$ weeks' gestation from maternal risk factors, estimated fetal weight Z-score at $35^{+0} – 36^{+6}$ weeks' gestation and estimated fetal weight growth velocity (top table) or abdominal circumference growth velocity (bottom table).

Screening test	Birthweight <10th percentile		Birthweight <3rd percentile	
	AUROC curve (95% CI)	DR at 10% SPR % (95% CI)	AUROC curve (95% CI)	DR at 10% SPR % (95% CI)
SGA within 2 weeks				
EFW Z-score at 35^{+0} - 36^{+6} weeks	0.938 (0.928, 0.947)	80.7 (77.6, 83.9)	0.943 (0.934, 0.952)	80.5 (77.2, 83.7)
Maternal risk factors	0.696 (0.673, 0.718)	29.1 (26.5, 32.4)	0.691 (0.663, 0.718)	28.1 (25.2, 31.6)
EFW growth velocity	0.670 (0.645, 0.694)	31.3 (28.4, 34.7)	0.694 (0.664, 0.725)	35.9 (32.3, 38.8)
EFW Z-score + EFW growth velocity + maternal risk factors	0.941 (0.932, 0.950)	82.5 (79.4, 85.3)	0.944 (0.935, 0.953)	79.2 (76.3, 82.6)
SGA at any stage				
EFW Z-score at 35^{+0} - 36^{+6} weeks	0.891 (0.885, 0.898)	65.3 (63.0, 67.7)	0.920 (0.913, 0.928)	73.3 (70.2, 76.1)
Maternal risk factors	0.709 (0.697, 0.720)	31.1 (28.6, 33.1)	0.712 (0.696, 0.729)	32.4 (29.7, 35.9)
EFW growth velocity	0.613 (0.600, 0.626)	21.2 (18.6, 24.4)	0.636 (0.617, 0.654)	25.4 (22.6, 28.7)
EFW Z-score + EFW growth velocity + maternal risk factors	0.902 (0.896, 0.908)	69.3 (66.8, 72.4)	0.927 (0.920, 0.934)	75.2 (72.4, 78.6)

Screening test	Birthweight <10th percentile		Birthweight <3rd percentile	
	AUROC curve (95% CI)	DR at 10% SPR % (95% CI)	AUROC curve (95% CI)	DR at 10% SPR % (95% CI)
SGA within 2 weeks				
EFW Z-score at 35^{+0} - 36^{+6} weeks	0.938 (0.928, 0.947)	80.7 (77.6, 83.9)	0.943 (0.934, 0.952)	80.5 (77.2, 83.7)
Maternal risk factors	0.696 (0.673, 0.718)	29.1 (26.5, 32.4)	0.691 (0.663, 0.718)	28.1 (25.2, 31.6)
AC growth velocity	0.722 (0.699, 0.745)	35.1 (32.0, 38.4)	0.747 (0.719, 0.775)	38.0 (35.1, 41.3)
EFW Z-score + AC growth velocity + maternal risk factors	0.941 (0.932, 0.950)	81.9 (78.3, 84.7)	0.944 (0.935, 0.954)	80.2 (77.7, 83.8)
SGA at any stage				
EFW Z-score at 35^{+0} - 36^{+6} weeks	0.891 (0.885, 0.898)	65.3 (63.0, 67.7)	0.920 (0.913, 0.928)	73.3 (70.2, 76.1)
Maternal risk factors	0.709 (0.697, 0.720)	31.1 (28.6, 33.1)	0.712 (0.696, 0.729)	32.4 (29.7, 35.9)
AC growth velocity	0.659 (0.647-0.672)	24.4 (21.3, 27.7)	0.689 (0.671-0.706)	30.0 (27.1, 33.6)
EFW Z-score + AC growth velocity + maternal risk factors	0.902 (0.896, 0.908)	69.2 (66.7, 72.3)	0.926 (0.919, 0.934)	75.9 (73.0, 78.8)

AUROC = area under the receiver operating characteristic curves; CI = confidence interval; EFW = estimated fetal weight; AC = abdominal circumference; SGA = small for gestational age; DR = detection rate; SPR = screen positive rate

Table 4. Screen positive rate necessary to achieve prediction of 85%, 90% and 95% of small for gestational age neonates delivering within two weeks and at any stage after assessment at $35^{+0}-36^{+6}$ weeks' gestation.

Screening test	Screen positive rate for detection rate of:		
	85% (95% CI)	90% (95% CI)	95% (95% CI)
SGA within 2 weeks			
SGA <10th percentile			
EFW Z-score at 35^{+0} - 36^{+6} weeks	16.6 (12.1, 15.2)	18.9 (17.2, 20.7)	26.4 (24.4, 28.4)
EFW Z-score + EFW growth velocity + maternal risk factors	12.0 (10.6, 13.6)	17.2 (15.6, 19.0)	27.1 (25.1, 29.2)
EFW Z-score + AC growth velocity + maternal risk factors	12.6 (11.1, 14.2)	17.7 (16.0, 19.5)	27.5 (25.5, 29.5)
SGA <3rd percentile			
EFW Z-score at 35^{+0} - 36^{+6} weeks	13.4 (12.0, 14.9)	16.7 (15.1, 18.3)	22.0 (20.3, 23.8)
EFW Z-score + EFW growth velocity + maternal risk factors	13.1 (11.7, 14.6)	16.1 (14.6, 17.7)	20.4 (18.7, 22.1)
EFW Z-score + AC growth velocity + maternal risk factors	13.1 (11.7, 14.6)	15.4 (13.9, 16.9)	20.1 (18.5, 21.9)
SGA at any stage			
SGA <10th percentile			
EFW Z-score at 35^{+0} - 36^{+6} weeks	21.2 (23.4, 25.0)	30.7 (29.9, 31.5)	43.0 (42.1, 43.9)
EFW Z-score + EFW growth velocity + maternal risk factors	22.2 (21.4, 22.9)	29.8 (29.0, 30.6)	40.0 (39.1, 40.8)
EFW Z-score + AC growth velocity + maternal risk factors	22.4 (21.6, 23.1)	29.4 (28.5, 30.2)	40.2 (39.3, 41.2)
SGA <3rd percentile			
EFW Z-score at 35^{+0} - 36^{+6} weeks	17.7 (17.1, 18.4)	23.1 (22.4, 23.9)	32.8 (32.0, 33.6)
EFW Z-score + EFW growth velocity + maternal risk factors	16.2 (15.6, 16.8)	20.8 (20.1, 21.5)	31.0 (30.2, 31.8)
EFW Z-score + AC growth velocity + maternal risk factors	16.2 (15.6, 16.8)	21.3 (20.6, 22.0)	31.0 (30.3, 21.8)

CI = confidence interval; SGA = small for gestational age; EFW = estimated fetal weight; AC = abdominal circumference.

Table 5. Prediction of adverse perinatal outcomes from multivariable logistic regression analysis demonstrating the contribution of abdominal circumference growth velocity <1st decile, in addition to the estimated fetal weight Z-score in pregnancies with estimated fetal weight below the 10th percentile at $35^{+0} – 36^{+6}$ weeks' gestation.

Variable	SGA <10th percentile OR (95% CI)	SGA <3rd percentile OR (95% CI)	Adverse perinatal outcome OR (95% CI)
EFW Z-score at 35^{+0} - 36^{+6} weeks	0.20 (0.16, 0.24) p<0.001	0.23 (0.19, 0.28) p<0.001	0.50 (0.43, 0.59) p<0.001
AC growth velocity <1st decile	0.84 (0.66, 1.05) P=0.123	0.98 (0.78, 1.24) P=0.884	1.15 (0.86, 1.55) P=0.343

EFW = estimated fetal weight; AC = abdominal circumference; OR = odds ratio; CI = confidence interval;